Remarks

In this response, Applicants have amended claims 30, 32, 37, 39, 44, 46 to comply with trademark citations. Applicants have amended claim 27 to overcome the rejection under 35 U.S.C. § 112, second paragraph.

Claim Objection

Applicants have amended claims 30, 32, 37, 39, 44, 46 which recite the trademarks TRIS and BRIJ-35 according to Examiner's suggestion.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 27-33 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants have amended claim 27 to overcome this rejection. Applicants respectfully submit that the metes and bounds of the claim are clear and request the §112 second paragraph rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Claims 27-29, 31, 33-36, 38, 40-43, 45, and 47 stand rejected under 35 U.S.C. §102(b) as being anticipated by Jensen et al. (WO 96/20005, July 15, 1996). Applicants respectfully disagree with the Examiner. In order to anticipate, a single reference must disclose each and every element of a claim. Applicants' pending claims are limited to a *solution* formulation and thus, Jensen does not anticipate Applicants' invention.

The Examiner states that Jensen discloses "a composition containing glucagon-like-peptide-1 (GLP-1), a pharmaceutically acceptable preservative, a tonicity modifier that is glycerol" citing pages 1-2, 7 and 10 of Jensen. Applicants respectfully disagree with the Examiner's overreaching interpretation of what Jensen discloses. Pages 1and 2 of Jensen suggest a need for a GLP-1 compound having protracted action. Jensen cites US 5,120,712 and EP 619,322 as other examples (polymers and crystals) of protracted action. Jensen discloses a composition that results in a gel which shows protracted release of the GLP-1 compound. In fact, Jensen distinguishes itself from the art by stating, "None of these known compositions are gels or thixotropic compositions." (Jensen, page 2, line 21). The common and ordinary meaning of thixotropic a property exhibited by certain gels of becoming fluid when stirred or shaken and returning to the semisolid state upon standing. Thus, it is clear that Jensen does not disclose a solution formulation.

Page 7 of Jensen discloses a zinc-free gel composition comprising GLP-1, glycerol, m-cresol at pH 7.2, and zinc containing gel compositions comprising GLP-1, Zn^{++}, glycerol, m-cresol at pH 7.4. Page 8 of Jensen discloses a zinc containing gel composition comprising GLP-1, Zn^{++}, glycerol, m-cresol at pH 8.7, and a non-gel, non protracted reference solution comprising GLP-1, glycerol, phenol at pH 7.3. Page 10 discloses a composition that is a gel. Applicants' invention is a shelf stable solution formulation comprising a GLP-1 molecule, a preservative; a tonicity modifier, and a pH that is about 8.2 to about 8.8. The Jensen reference does not anticipate Applicants' invention.

The Examiner states that Jensen discloses "the composition can be in the form of a solution or as part of a gel or foam" and cites page 10 of Jensen. Applicants cannot find this disclosure anywhere in Jensen, especially on page 10. Jensen does state in Example 5 that "a *non-gel*, non-protracted solution of GLP-1(7-37) for use as a reference in the absorption studies, the following low concentrated zinc free GLP-1(7-37) composition designated REF was chosen: 1 mg/ml GLP- 1 (7-37), 16 mg/ml glycerol, 3 mg/ml phenol (*pH value: 7.3*)" (Jensen, page 8, lines 9-13). Implicit in this statement is that a solution formulation comprising GLP-1 glycerol, and phenol requires a different pH to be a solution formulation because at pH. Jensen also states, "the compositions of this invention are considerably more protracted than the reference solution." (Jensen, page 9, lines 23-24). Clearly, Jensen is suggesting that his compositions are not *solutions*.

The Examiner states that Jensen discloses "a composition having a pH of 8.7 that falls within the range of pH recited in claims 27, 28, 35 and 41-42 (page 8 of the reference)." Example 4 of Jensen states, "This composition was made by mixing 1 ml of GLP-1(7-37) solution (40 mg/ml), adjusted to a pH value of 8.7, with a 1 ml of a solution containing 6 mg/ml m-cresol, 32 g/l glycerol, and 4 mmol/l zinc acetate. A high viscosity gel was formed soon after mixing." Jensen discloses a high viscosity gel and not a solution. Applicants' invention is a stable solution formulation that is not anticipated by Jensen. Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 103

The subject matter of the claims was commonly owned at the time the invention was made, therefore 35 U.S.C. 103(c) and the potential 35 U.S.C. 10(e), (f), or (g) prior art under 35 U.S.C. 103(a) is not applicable.

Claims 27-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over

Andrews et al. (WO 93/25579, December 23, 1993) in view of Jensen and Smith (U.S. Patent No. 5,908,830, October 30, 1997).

Applicants respectfully disagree that the Examiner has supported a *prima facie* case of obviousness. The Examiner has not established the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve Applicants' claimed invention. Applicants request reconsideration and withdrawal of this rejection.

Andrews discloses derivatives of GLP-1, truncated GLP-1, insulinotropin, and truncated insulinotropin that have a pI of about 4 or less or a pI of about 7 or greater that are particularly suited for iontophoresis delivery. Andrews also discloses pharmaceutical compositions of these compounds that are useful for enhancing insulin action by iontophoresis delivery. According to Andrews, iontophoresis is a method of transdermal administration. It involves the application of a potential electrical gradient of different voltage patterns, such as electroporation or pulsed currents, across the skin in conjunction with the surface co-application of therapeutic agents. Andrews does not disclose a buffering agent on page 1. Andrews discloses the desire of the polypeptide derivative in a solution, gel, or foam to have the same or approximately the same charge as the electrode in the drug reservoir of the iontophoretic device to be employed. The charge can be controlled by the use of an appropriate buffer. However, there is neither a suggestion or motivation to use a shelf stable solution formulation, nor a disclosure of how to prepare such a shelf stable solution formulation. No pH range is mentioned, no preservative is mentioned, and no tonicity modifier is mentioned. In fact Andrews actually discloses, "In general, to achieve the highest transport efficiency by iontophoresis with such compositions, it is preferable to minimize the concentration of all ionic species except the polypeptide derivative." (Andrews page 10 line 33 to page 11, line 2). Therefore, Andrews would teach away from using preservatives and tonicity modifiers.

The Examiner states that Jensen "teaches a pH that falls within the claimed range." Example 4 of Jensen states, "This composition was made by mixing 1 ml of GLP-1(7-37) solution (40 mg/ml), adjusted to a pH value of 8.7, with a 1 ml of a solution containing 6 mg/ml m-cresol, 32 g/l glycerol, and 4 mmol/l zinc acetate. A high viscosity gel was formed soon after mixing." As previously stated, Jensen discloses a gel composition, not a solution.

Jensen goes on to say, "Surprisingly, it has been found that compositions containing a GLP-1 compound and a phenolic and/or alcoholic aromatic compound in certain concentrations result in a thixotropic gel showing a protracted release of the active GLP-1 compound." (Jensen, page 3 lines 2-5). Implicit in this statement is the fact that if

Applicants follow Jensen, Applicants would expect to arrive at a gel composition that would have a protracted profile and not produce a stable solution formulation.

The Examiner states that the Smith reference (U.S. Patent No. 5,908,830, October 30, 1997) teaches the use of TRIS buffer in a combination therapy for the treatment of diabetes. The Smith reference relates generally to a combination therapy and does not suggest a shelf stable solution formulation at the claimed pH range. TRIS buffer at pH 8 is found in Example 1 and it is used to resuspend OB (obesity) protein. TRIS buffer at pH 7.6 is found in Example 2 and it is used in an immunodetection assay of the OB gene product. Smith does not mention the buffer or pH as being useful for a shelf stable formulation of GLP-1 molecules.

Applicants' invention is a *solution* formulation that has different attributes than a protracted formulation. Applicants' stable solution formulation is rapidly absorbed by the body. It does not have the properties of a gel having protracted action. Applicants suggest that this stable solution formulation is useful in delivery devices that expose this formulation to elevated temperatures and/or mechanical stress. (See Specification page 6). "For example, stable GLP-1 formulations are required for use in continuous infusion systems and pen delivery devices. Current formulations provide only limited stability in these types of delivery devices." (Specification page 6, 2nd paragraph). The patient's body heat and body motion, and turbulence in the tubing and pump impart a relatively high amount of thermo-mechanical energy to the formulation. In the interest of minimizing the frequency with which the reservoir is refilled, and of minimizing the size of the reservoir, formulations having a relatively high concentration of the therapeutic agent are advantageous. (Specification page 6, 3rd paragraph).

Applicants describe their solution formulation as 'stable.' 'Stable' refers to both chemical as well as physical stability. The Specification states, "Physical stability refers to properties such as protein aggregation, which can be measured by a sample's attenuation of light. The measurement relates to the turbidity of a formulation. Turbidity is produced by aggregation or precipitation of proteins or complexes in the formulation and is indicative of decreased stability of a *solution* formulation. The more turbid a protein preparation, the less stable the preparation is. Stability also refers to the chemical stability of the formulation such as the propensity of the proteins to form high order polymers which is indicative of decreased stability." (Emphasis added, Specification page 6, 3rd paragraph).

In order to support a regulatory submission, stability studies need to be performed to demonstrate safety and efficacy. A solution formulation that ultimately gels or precipitates

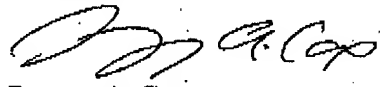
will not demonstrate the same physical properties as it did as a solution. The active ingredient's absorption properties change. The pharmacokenetics and pharmacodynamics change. Further, it is known in the art that GLP-1 molecules in gel or precipitate formulations can cause injection site reactions. Applicants' invention is a stable solution formulation that will support a regulatory submission.

The cited references alone or in combination do not provide a shelf stable solution formulation. There is absolutely no suggestion or motivation to combine these references. In fact these references try to solve completely different problems. Andrews suggests polypeptides that can be delivered by iontophoresis, Jensen suggests gel compositions that have protracted action, and Smith suggests a combination therapy. The Examiner is merely picking different elements out of these references without any suggestion or motivation to use these references to arrive at Applicants' claimed invention. Thus, a case of obviousness cannot be supported.

SUMMARY AND CONCLUSION

Applicants respectfully assert that the application is now in condition for allowance. The claims are definite and particularly point out and distinctly claim the subject matter being sought. The shelf stable solution formulation is neither anticipated nor obvious in view of the cited references. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,



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